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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/810,486

03/26/2004

Mitsuru Furusawa

690116.401C1

8553

32642 7590 02/19/2009

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EXAMINER

BURKHART, MICHAEL D

ART UNIT

PAPER NUMBER

1633

MAIL DATE

DELIVERY MODE

02/19/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/810,486	<b>Applicant(s)</b> FURUSAWA, MITSURU	
	<b>Examiner</b> MICHAEL BURKHART	<b>Art Unit</b> 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 8/9/2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) 3,5,32,39,40,48,50,77,84,85,95-125,127-129 and 146 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 9, 12-14, 16, 17, 33, 36, 45, 54, 55, 61, 62, 78, 81, 126, 130, 131, 133-137 and 140-145 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>5/22/08; 6/4/08</u> | 6) <input type="checkbox"/> Other: _____  |

Continuation of Disposition of Claims: Claims pending in the application are 1,3,5,9,12-14,16,17,32,33,36,39,40,45,48,50,54,61,62,77,78,81,84,85,95-131,133-137 and 140-146.

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### **DETAILED ACTION**

Receipt and entry of the amendment dated 8/9/2008 is acknowledged. After entry of the amendment, claims 1, 3, 5, 9, 12-14, 16, 17, 32, 33, 36, 39, 40, 45, 48, 50, 54, 55, 61, 62, 77, 78, 81, 84, 85, 95-131, 133-137 and 140-146 are pending. Claims 3, 5, 32, 39, 40, 48, 50, 77, 84, 85, 95-125, 127-129 and 146 remain withdrawn as directed to non-elected inventions. Claims 1, 9, 12-14, 16, 17, 33, 36, 45, 54, 55, 61, 62, 78, 81, 126, 130, 131, 133-137 and 140-145 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

### ***Claim Objections***

Claim 134 is objected to because of the following informalities: the claim is dependent upon either claim 132, claim 1, or both. Claim 132 has been cancelled. Appropriate correction is required. In the interest of compact prosecution, the claim has been interpreted to be dependent upon claim 130, from which claim 132 previously depended and into which the limitations of canceled claim 132 have been amended.

Claims 135-137 and 145 are objected to because of the following informalities: the claims are dependent upon claim 132 which has been cancelled. Appropriate correction is required. In the interest of compact prosecution, the claims have been interpreted to be dependent upon claim 130, from which claim 132 previously depended and into which the limitations of canceled claim 132 have been amended.

### *Specification*

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: the specification does not provide antecedent basis for the term "a rate of  $10^{-6}$  or greater" as found in claims 1, 45, 51, 126, and 130. **This objection is maintained for reasons et forth in the Office Action dated 2/8/2008 and for reasons set forth below.**

### *Response to Arguments*

Applicant's arguments filed 8/9/2008 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) ¶ [0577] of the published application provides support and antecedent basis for this claim limitation; 2) mutation rates of  $10^{-3}$  or  $10^{-2}$  are disclosed and supply support and antecedent basis for mutation rates greater than  $10^{-6}$ .

Regarding 1) and 2), the disclosed mutation rates of  $10^{-2}$  or  $10^{-3}$  do not provide support or antecedent basis for the limitation of providing "mismatched bases at a frequency of  $10^{-6}$  or greater." A frequency of  $10^{-6}$  is considered to be one mismatched base per million bases. Thus, a frequency of  $10^{-2}$  is a frequency of one mismatched base per one hundred bases: a frequency that is lethal to yeast (at the least) for reasons found in the enablement rejections of record. What was meant by "a frequency of  $10^{-6}$  or greater" in the enablement rejections was, for example, frequencies of  $10^{-7}$  or  $3 \times 10^{-6}$ : stated differently, one mismatched base in 10 million or one mismatched base in 3 million bases, respectively. Thus, the disclosure applicants rely upon to provide antecedent basis and support for the claim limitation " $10^{-6}$  or greater" discloses mutation frequencies going in the opposite direction of those claimed and considered enabled.

***Information Disclosure Statement***

The information disclosure statement filed 6/4/2008 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The references for which a copy has not been supplied have been lined through and have not been considered.

***Claim Rejections - 35 USC § 102***

Claims 130, 131, 133-137, 140 and 145 are rejected under 35 U.S.C. 102(b) as being anticipated by Kokoska et al (Mol. Cell. Biol., 2000, of record) as evidenced by Burgers (Chromosoma, 1998, of record). **This is a new rejection necessitated by amendment of the claims in the response dated 8/9/2008. Specifically, the claims have been amended to recite the use of an expression vector, a limitation not found in any previously examined claims.**

Kokoska et al teach yeast strains comprising temperature sensitive mutations of the *POL3* (DNA polymerase  $\delta$ ) gene which, *inter alia*, is involved in 3'-5' exonuclease proofreading of gene replication errors (see abstract and page 7490, first and second columns). Yeast cells were transformed with plasmids expressing the *pol3* mutants, which are considered to be expression plasmids because they expressed the *POL3* genes (*POL3* is taught to be an essential gene innate to yeast (page 7492, second column), and the native *POL3* promoter was replaced with a *GALI/10* promoter for some experiments, see ¶ bridging pages 7498-7499). The mutator yeast were then used to provide mutations in the *CAN1* locus. The cells acquired canavanine

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resistance upon selection (i.e. a desired hereditary trait). See page 7492, second column, first full ¶ to page 7493, last ¶, and Table 2. Some *pol3* mutants comprised alterations in the POL3 active site (Fig. 1, ts1 in particular, Fig. 1 also teaches the *pol3-01* mutation known in the art to have changes in the active site). The *pol3-ts* mutants had a mutation rate (i.e. provided at least one mismatch) of  $\sim 10^{-6}$  (Table 2). Burgers teaches that yeast DNA polymerase delta exists as a dimer inherently involved in leading and lagging strand DNA replication (page 218, the abstract, Figs. 1 and 2).

### ***Claim Rejections - 35 USC § 103***

Claims 1, 9, 12-14, 16, 17, 33, 36, 45, 54, 55, 61, 62, 78, 81, 126, 141, and 142-144 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kokoska et al (2000, as above) and Burgers (1998, as above) in view of Morrison et al (1993, of record), Tanabe et al (EP 1 054 057, 2000, cited by applicants) and del Cardayre et al (U.S. 6,379, 964, filed 7/15/1999, of record).

**This is a new rejection necessitated by amendment of the claims in the response dated 8/9/2008. Specifically, the claims have been amended to recite the use of an expression vector, a limitation not found in any previously examined claims.**

The teachings of Kokoska et al and Burgers are as above and applied as before. In addition, Morrison et al teach that yeast bearing the *pol3-01* mutation (also taught in Kokoska et al, see above), or mutations in *PMS1*, exhibit a spontaneous mutator phenotype (page 1467, ¶ linking first and second columns). The *pol3-01* mutant grew substantially as well as wild-type (compare + and - colonies in Fig. 2A). Absent evidence to the contrary, the proofreading function of *POL3* detects errors in the daughter strand of a replication fork, not the parent strand,

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thus the *pol3-01* mutant would "provide" a difference in the number of errors of one strand (the daughter strand) relative to the parent strand, e.g. as in claim 55. Upon growth under selective conditions, the *pol3-01* mutant provided a number of mismatch mutations in the URA3 gene, some of which involved two changes of the wild-type sequence (Table II). The *pol3-01* mutant had a mutation rate (i.e. provided at least one mismatch) of  $\sim 10^{-6}$  (Table I). The cells acquired a 5-fluoro-orotic acid resistance upon selection (page 1467, second column, last ¶, and Table II), i.e. a desired hereditary trait. The yeast cells were transformed with a plasmid bearing the mutant *pol3-01* mutant, i.e. an exogenous DNA polymerase, e.g. claims 138, 139 (see Fig. 1, page 1467, second column, second full ¶).

Neither Morrison et al, Kokoska et al or Burgers teaches the method step of selecting for a high temperature resistant yeast cell.

Tanabe et al teach the use of mutator strains of cells or organisms to mutagenize genes and select for a given mutant under desired pressure conditions. Certain mutator genes disclosed are several DNA polymerase subunits. See ¶'s [0009]-[0016].

del Cardayre et al teach the selection of cells or organism for the evolution of desired properties (abstract). Yeast strains having a mutator phenotype are disclosed as useful for the methods of del Cardayre et al, with mutations in mismatch repair genes, such as *PMS1*, being one specific example. See column 51, line 57 to column 52, line 48. One desired property disclosed by del Cardayre for selection in yeast cells is thermotolerance, for use in fermentation applications. See column 59, lines 63-65 and column 60, lines 15-22. Certain thermotolerant *S. cerevisiae* strains are proposed as starting points for selection of the desired yeast (column 61, lines 27-45). Method steps for selection of thermotolerant yeast are disclosed, and include



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selecting for strains able to grow after a heat treatment or growth at elevated temperatures. See column 62, line 41 to column 63, line 18.

The claimed methods of producing a high temperature resistant yeast cell by increasing the error-prone frequency of DNA polymerase delta are essentially taught by Kokoska et al with the exception of the step of selecting and isolating a high temperature resistant yeast cell. The ordinary skilled artisan, seeking a method to develop thermotolerant yeast strains for use in ethanol fermentation, would have been motivated to select the mutator yeast strains of Kokoska and Morrison et al (*pol3-01* mutant) for high temperature resistance because both Tanabe and del Cardayre et al teach mutator strains of yeast to be useful for selecting a desired trait of an organism. del Cardayre et al further suggests that thermotolerance is one such desired trait in yeast. The skilled artisan would also realize that the temperature sensitive *POL3* mutants of Kokoska et al would not be suitable for use at higher temperatures, but that the *pol3-01* mutant disclosed by Morrison and Kokoska et al is not temperature sensitive and thus would be suitable. It would have been obvious for the skilled artisan to select the mutator strains of Kokoska and Morrison et al for high temperature resistance because of the known benefit of generating thermotolerant yeast for use in ethanol fermentation as taught by del Cardayre et al.

Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

***Response to Arguments***

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Applicant's arguments filed 8/9/2008 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) Morrison et al and Burgers do not teach the use of a plasmid vector to express a DNA polymerase, but rather, teach the use of a yeast strain with a chromosomal DNA polymerase.

Regarding 1), Kokoska et al teach the transformation of yeast with expression vectors encoding the DNA polymerase for reasons set forth above.

### ***Double Patenting***

Claims 1, 9, 12-14, 16, 17, 33, 36, 45, 54, 55, 61, 62, 78, 81, 126, and 130, 131, 133-137, and 140-145 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,2, 4, 6-47, 49, 51-76, 78-83, and 86-89 of copending Application No. 10/550,924. **This rejection is maintained for reasons made of record in the Office Action dated 5/31/2007, 2/8/2008, and for reasons set forth below.**

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### ***Response to Arguments***

Applicant's arguments filed 8/9/2008 have been fully considered but they are not persuasive. Applicants essentially assert that the rejection has been noted. Hence, the rejection stands until the claims of either application do not render each other obvious.

***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHAEL BURKHART whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Burkhardt/  
Primary Examiner, Art Unit 1633